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51. (Canceled Herein)

52. (Currently Amended) A method executed by a computer under the control of a program, said computer including a memory for storing said program, said method comprising the steps of:

(A) receiving a protein backbone structure with variable residue positions of a desired target protein, said protein structure comprising:

- i) a protein template structure comprising a protein backbone structure and at least one non-variable residue; and
- ii) a plurality of variable residue positions;

(B) establishing a group of potential amino acids side chains for each of said variable residue positions, wherein the group of potential amino acids side chains for at least one of said variable residue position has an amino acid side chains selected from each of at least two different amino acid side chains; and

(C) analyzing the interaction of all or part of each of said potential amino acids side chains from said group with all or part of the remainder of said protein backbone structure to generate a set of optimized proteins sequences.

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53. (NEW) A method according to claim 29 or 52 wherein said analyzing step comprises a DEE computation.

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54. (NEW) A method according to claim 28, 29, or 52 wherein said set of optimized protein sequences comprises the globally optimal protein sequence.

55. (NEW) A method according to claim 28 or 53 wherein said DEE computation is selected from the group consisting of original DEE and Goldstein DEE.

56. (NEW) A method according to claim 28 or 53 wherein said analyzing step includes the use of at least one scoring function.

57. (NEW) A method according to claim 56 wherein said scoring function is selected from the group consisting of a van der Waals potential scoring function, a hydrogen bond potential scoring function, an atomic solvation scoring function, an electrostatic scoring function and a secondary structure propensity scoring function.

58. (NEW) A method according to claim 57 wherein said analyzing step includes the use of at least two scoring functions.

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59. (NEW) A method according to claim 57 wherein said analyzing step includes the use of at least three scoring functions.

60. (NEW) A method according to claim 57 wherein said analyzing step includes the use of at least four scoring functions.

61. (NEW) A method according to claim 57 wherein said scoring function is an atomic solvation scoring function.

62. (NEW) A method according to claim 57 wherein said atomic solvation scoring function includes a scaling factor that compensates for over-counting.

63. (NEW) A method according to claim 28, 29, or 52 further comprising experimentally testing at least one member of said set.

64. (NEW) A method according to claim 54 further comprising the step of:
generating a list of additional optimal sequences from said globally optimal protein sequence.

65. (NEW) A method according to claim 63 wherein said generating includes the use of a Monte Carlo search.

66. (NEW) A method according to claim 28, 29, or 52 wherein said analyzing step comprises a Monte Carlo computation.

67. (NEW) A method according to claim 63 further comprising the step of:
testing some or all of said protein sequences from said list to produce potential energy test results.

68. (NEW) A method according to claim 67 further comprising the step of:
analyzing the correspondence between said potential energy test results and theoretical potential energy data.

69. (New) A method executed by a computer under the control of a program, said computer including a memory for storing said program, said method comprising the steps of:

- (A) receiving a protein structure of a desired target protein, said protein structure comprising:
i) a protein template structure comprising a protein backbone structure and at least one non-variable residue; and

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ii) a plurality of variable residue positions;

- (B) establishing a group of potential amino acid side chains for a plurality of variable residue positions of said protein, wherein at least one of said amino acid side chains is from a hydrophilic amino acid; and
(C) analyzing the interaction of all or part of each of said potential amino acid side chains from said group with all or part of said protein structure to generate a set of optimized proteins sequences, wherein said analyzing step includes the use of at least one scoring function.

70. (New) A method according to claim 56 wherein said hydrophilic amino acid is selected from the group consisting of serine, threonine, aspartic acid, asparagine, glutamine, glutamic acid, arginine, lysine, and histidine.

71. (New) A method according to claim 28, 29, 52, or 71 further comprising modulating the protein backbone structure.

72. (New) A method according to claim 28, 29, 52, or 71 wherein said variable residue positions comprise one or more non-core positions.

73. (New) A method according to claim 28, 29, 52, or 69 wherein at least one scoring function is used at a first variable position and at least one scoring function is used at a second variable position, wherein said scoring functions are different.

74. (New) A method according to 28, 29, 52, or 69 wherein step (c) comprises a second group for a second variable position has a second set of at least two amino acid side chains,

75. (New) A method according to 76 wherein said first and second amino acid side chains are different.

76. (New) A method according to 76 wherein said first and second amino acid side chains are the same.

77. (New) A method according to 28, 29, 52, or 69 wherein said non-variable residues are fixed.

78. (New) A method according to 28, 29, 52, or 69 wherein said non-variable residues are floated.

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79. (New) A method according to claim 28, 29, 52, or 69 wherein said variable residue positions are structurally functional residue positions.

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80. (New) A method according to claim 28, 29, 52, or 69 wherein said variable residue positions are biologically functional residue positions.
